Q1-1 / Keratinization of Keratinocytes & its Disorders ?

→ **Keratinization** → Transformation of nucleated basal Columnar cells to → flat, anucleated, dead Corneocytes during their descent Through epidermis

→ Characteristic changes occur in keratinocytes

1. losing nuclei & cytoplasmic organisms
2- Become filled ē tens. filaments of Matrix Ptn. "filaggrin"

→ Cytoskeleton of all mammalian cells Composed of 3 filament system.
- Micro filament → actin
- Micro tubules → tubulins
- intermediate filaments → keratins → The largest group of IF expressed by epithelial cells → form the Major Component of epidermis « skin, hair, Nail.

→ In basal cell layer → Expression of K_5 & K_{14} IF

→ In spinous cell layer → ↑ Expression of K_1 & K_{10} undergo upregulation
2) keratin poly peptides Polymerized → KIF
3) KIF aggregate into bundles

→ In granular cell layer; 1) KIF Continue to aggregate int. large bundles
2) Keratohyalin granules appear.
3) ↓ Metabolic activity & loss of cytoplasmic organelles of keratinocytes.
4) lamellar granules appear.

→ Keratohyalin granules → • produce profilaggrin

Profilaggrin ← Phosphatase enz from lamellar granules → filaggrin → aggregate KIF into large bundles « Macrofibrils
→ get them into parallel rou
Form matrix Ptn of Ks

Q1-2

→ formation of cell envelop

- starts in upper spinous cell layer
- ↑ intra cellular Ca^{++} influx activate → Trans glutaminase catalyze cross linked scaffold ptns : Lorcrin, involucrin, envoplakin, periplakin
- ω hydroxy ceramides from lamellar granules → bind to scaffold ptns & replace cell Membrane

→ In Cornified Horney layer : keratinocytes are dead.

In lower ST. Corneum

→ keratinocytes Composed of :

- plasma membrane . surrounding → impermeable cell envelop → packed & keratin macrofibrils & filaggrin

in upper ST Corneum.

- plasma membrane become discontinuous → replaced by
  - CE . insoluble & impermeable so → protect against environmental hazards
  - CE packed & Macrofibrils of filaggrin.
  - Corneocytes imbedded in intercellular material : lipid lamellae from lamellar granules so →

→ ST. Cornum appears as briks & Mortar Cement
" Corneocytes of lipid lamellae & cholesterol Sulfate "

→ hydrolysis of cholesterol sulfate (steroid sulfatase from keratinocyte granules) → Cholesterol → activate proteolytic degradation of desmosomes → separation of Corneocytes → desquamation.

Q 1-3 | Disorders of keratinization ?

due to defect in manufacture or desquamation of keratinocyte ?
leading to [1] Scaling [2] dyskeratosis.

[1] | Scaling | [3] abnormal keratin gene expression

Hyperproliferative

- Failure of desquamation to Compensate rapide rate of St. Corneum formation
- ↑ Mitotic figures
- Short epidermal Transit time
- Psoriasis, Epidermolytic Ichthyosis, Congenital Ichthyosiform erythroderma

Normoproliferative

- Retension hyperkeratosis
- ↑ inter Corneal Cohesion
- Normal Mitotic index
- Normal epidermal transit time
- Ichthyosis Vulgaris $\xrightarrow{dT}$ defect in profilaggrin
- X linked ichthyosis $\xrightarrow{dT}$ ↓ cholesterol sulfatase enzyme

[2] | dyskeratosis

Acantholytic "Corps ronds"

acantholytic cell show → Central homogenous, basophilic, pyknotic Nucleus
- Surrounded by clear halo
- peripheral to the halo → basophilic, dyskeratotic material « K bundle Collapsed »
→ Darieris Ds, Warty dyskeratoma, focal acantholytic dyskeratosis
- Transient acantholytic dermatosis,
- Hailey-Hailey Ds

Neoplastic

- Homogenous, eosinophilic bodies é remnants of Nuclei may be found — as in
- Bowenis Ds,
- Solar keratosis, SCC
- Keratoacanthoma —

Y1 - 2

3 | abnormal keratin

↓

Genetic defect in keratin gene

leading to AD disorders é epidermal fragility & blistering

↓

abnormal keratin expression

- k_6, k_{16} in → psoriasis
- k_8, k_{18} in → Epidermal tumours

Disease	Mutation of keratin gene.
- Epidermolysis Bullosa Simplex	k_5, k_{14}
- Epidermolytic Ichthyosis	k_1, k_{10}
- Superficial epidermolytic Ichthyosis	k_2
- Epidermolytic palmo-plantar keratoderma (EPPK)	k_9
- Diffuse non epidermolytic ppk	k_1
- Focal non epidermolytic ppk	k_{6c}
- white Spongey nevus	k_4, k_{13}
. Monilethrix	k_{81}, k_{83}, k_{86}
. Pachyonychia Congenita	Type I → k_{6a}, k_{16} Type II → k_{6B}, k_{17}

Q2-1 / Congenital Ichthyosis ?

- Epidermolytic Ichthyosis · BCIE
- Non bullous Cong. Ichthyosiform erythroderma (NBCIE)
- lamellar ichthyosis
- Harlequin ichthyosis
- superficial epidermolytic ichthyosis
- Ichthyosis en Confetti
- Ichthyosis hystrix

Ichthyosiform Syndromes

- Sjogren · larsson syndrome
- Rudis syndrome
- Conradis syndrome
- Netherton syndrome
- Tay's "PIBIDS" synd.
- CHILD syndrome
- Dorfman Chanarin synd.

Ichthyosiform syndromes

→ Sjogren larsson syndrome → LI, mental retardation, spastic paresis
· due to fatty aldehyde dehydrogenase deficiency (FALDH)

→ Rudis syndrome → LI, mental retardation, Hypogenadism, Acanthosis Nigricans

→ Conradis syndrome → Ichthyosis "whorled pattern", Cataract, cicatricial alopecia, CVS abnormality, mental Retardation, dt peroxisomal enz ↓

→ Netherton syndrome → Ichthyosis linearis circumflexa, Atopy, Trichorrhexis invaginata

→ PIBIDS syndrome → photosensitivity, CIE, Brittle hair, intelectual impair, Decreased fertility, short stature.

- CHILD syndrome → Congenital hemidysplasia, ichthyosiform erythroderma, limb defect.

- Dorfman · chanarin syndrome → CIE like or Collodion Baby, Myopathy, Cataract, neurological problems, fatty liver
dt → long chain lipase deficiency —

	Epidermolytic Ichthyosis BCIE	Cong. Ichthyosiform erythroderma - ARCIE	lamellar Ichthyosis	Harlequin Ichthyosis
incidence	Rare	Rare	Rare	Rare.
inheritance	AD	AR	AR	AR.
onset	birth → erythema, scaling bullae, denudation	Birth: Collodion Baby cracks + peeling occur	Collodion Baby	- premature Baby in Enclosed in hard, Thick ST. Corneum
Course	improve but hyperkeratosis persist	may improve	persist	fatal ∈ in 1ST week of life.
Clinically. scles	- Thick, brown, verrucous "cobble stone pattern" - Generalized & flexural accentuation furrow - hyperkeratosis	fine, white scales & erythroderma	- large, Thick, dark, plate like, No erythroderma - Generalized effect face, flexures	- Crack in Thick membrane → Yellow adherent plates separated, deep, red fissure
associations	→ infection → bad odour PPK, Nail dystrophy, Abnormal gait + posture	- PPK, Scaring alopecia, ectropion, Heat intolerance, Chanarian Dorfman, Syndrome	PPK, Sparse scalp hair marked ectropion, Chanarian Dorfman, syndrome - hypohydrosis	- infection → sepsis - marked ectropion - Flat ear - Hand + feet oedema, swelling, auto amputation
H/P.	Epidermolytic hyperkeratosis - in ST granulosum → unclear cell wall - Nuclei surrounded by clear halo - hypergranulosis + hyperkeratosis	- hyperkeratosis, parakeratosis acanthosis, hypergranulosis - PAS + lectin +ve EM → ↑ lamellar bodies ↑ Lipid droplets abnormal inter cellular lipid lamellae	- Compact hyperkeratosis - granular longer → Normal - Mild acanthosis - PAS + lectin → -ve	- Thick. Compact ST. Corneum - follicular hyperkeratoses - EM → No abnormal lamellar, granules or lipid lamellae.
Pathogenesis	hyperproliferative - hyperkeratosis mutation in K1 K10 ↑ cell kinetics	- Mutation in TGM1 TALOXE3 ABCA12 gene - ↑ n-alkans in scales - ↑ cell kinetics	- Mutation in TGM1, ABCA12, cyp4F22 - Defect in Transglutaminase → abnormal CE - Normal cell kinetics	- Mutation ABCA12 gene. - absence lamellar granules → ↓ Lipid lamellae + PM phosphatase → failure ↓ desquamation → Normal kinetics

Q2-3

Superficial epidermolytic Ichthyosis

(Ichthyosis Bullosa of Siemens) → AD, Mutation KRT2

- EI like but → sparing palm & sole
- Mild hyper keratosis / denuded areas & Collarette borders "molting"

Ichthyosis en Confetti

- AD ← Mutation in KRT10 gene
- Ichthyosiform erythroderma < PPK since birth.
- Confetti like islands of Normal skin (متناثرة الجزر)

Ichthyosis hystrix

- marked hyperkeratosis & verrucous surface or protruding → porcupine like spines
  Common & EI

Tx :- Put Baby in humidified incubator and Monitor for Temp / Electrolytes / Infection.

- Avoid manual Scale removal or Topical keratolytics due to ↑ infection or percutaneous absorption
- use wet Compresses and light emollients
- Ceramide Containing lipid cream.

Acquired Ichthyosis

Occurs later in life.

[1] Malignancy: Lymphomas (Hodgkin's mainly), Kaposi's Sarcoma

[2] Nutritional Diseases:
- → Malnutrition, malabsorption diseases
- → Vit A Def → Linoleic acid Def
- → arachidonic A. Def → scaling + erythema

[3] Drugs: → Hypocholesterolemic Drugs
- → Nicotinic acid
- → oral Retinoids
- → Antiandrogens.
- → Maprotiline

[4] Environmental: Xerosis

[5] Immunological Disorders: SLE + Dermatomyositis.

[6] Endocrine Disorders: Hypothyroidism, Panhypopituitarism

[7] Infection: Leprosy and HIV

[8] Chronic ~~infection~~ inflammation: Sarcoidosis, Hepatic, Renal pt.

q3,4

Geno Q6

Q6 Compare ichthyosis vulgaris & X-linked ichthyosis

	Ichthyosis vulgaris (IV)	X-linked ichthyosis.
Incidence	Common.	uncommon [1:6000 ♂]
Inheritance	A.D.	XL Recessive boy only
onset	3-12 month of age.	< 3 months
Course	Improves	persist.
Clinical:		
Scales	small, fine, shiny white to translucent.	large, dark brown, dirty, tightly adherent
Distribution.	→ Extensor of extremities, sparing flexures [due to humidity produced by skin folds] → Hyperlinear palms & Soles → Furrowed heels.	More generalized affecting trunk, neck & flexures - sparing face.
Appearance at birth	Normal	Normal or scaly (in 1/3)
Association	- Atopy (50%) - Keratosis Pilaris - palmoplantar Keratosis (mild)	→ Corneal opacities → Cryptorchidism 12 → ♀ carrier: Corneal opac - Prolonged labour c affected child

Geno Q6

(2)

	Ichthyosis Vulgaris	X-linked ichthyosis
Histo-Pathology	- Moderate hyperkeratosis or absent granular layer. - E.M: Abnormalities of Keratohyaline granules	→ Hyper Keratosis → Normal or thick granular cell layer
Diagnosis	→ Clinical picture. → Diminished/absent stratum granulosum → Absent/reduced FLG immunostaining → Molecular testing	→ lipoprotein electrophoresis: increased mobility of B fraction → Increased plasma cholesterol sulphate. → Decreased steroid sulphatase activity in the leukocytes. → Molecular testing: eg FISH & array CGH

Geno Q6

(3)

	Ichthyosis vulgaris	X-linked ichthyosis
Pathogenesis	Retention hyperkeratosis	Retention hyperkeratosis
cell → Normal Kinase →	Deficiency of serine protease → persistance of Dsg-1 → abnormal persistance of desmosomes → retention hyperkeratosis → Mutations in FLG gene which encodes profilaggrin. Defective filaggrin → impairs barrier function, increases transepidermal water loss → severe xerosis.	→ Normal → Deletion of STS-gene → Steriod sulfatase deficiency in epidermis → accumulation of cholesterol sulfate. (product of barrier granules) that may inhibit proteolytic degradation of desmosomes via inhibition of transglutaminase → retention hyperkeratosis → Steroid sulphatase deficiency in placenta → inadequate deconjugation of DHEAS → low or absent estrogen → insufficient dilatation of CX → labor fails to initiate spontaneous or to progress (may need Cesarean Section).

	Recessive X-linked Ichthyosis	Lamellar Ichthyosis
Incidense	uncommon (1 - 6000) males	Rare (1 : 300,000)
Inheritance	XLR (boys only)	AR
Onset	< 3 months	at Birth or few weeks after
Course	Persists	persists
Clinically	- Large, dark, brown dirty scales - Trunk, neck, flexures sparing Face - Associated with ⇒ Corneal opacity ⇒ Cryptorchidism	- large thick, dark plate like with no or mild erythroderma - Generalized affecting Trunk, face, flexures - associated with → marked ectropion → crumpled ears → PPK → Hypohidrosis → sparse scal hair

q7

	Recessive x-Linked Ichthyosis	Lamellar Ichthyosis
Histopathology	- Moderate Hyperkeratosis - Normal or thick granular cell layer	Compact hyperkeratosis Normal granular layer mild acanthosis
Pathogenesis	Retention hyperkeratosis - decreased or absent Steroid sulfatase	Mutation in (Transglutaminase 1) ⇒ abnormal cell envelope
Diagnosis	- Lipoprotein electrophoresis → ↑ mobility of β-fraction - ↑ plasma cholesterol sulfate - ↓ steroid sulfatase activity in leukocytes - Molecular Testing (FISH - CGH)	- CIP - EM - Molecular testing In situ TGH1 assay.

(8) Darier's disease

= Keratosis follicularis

. It is an autosomal dominant disorder

. Young adult

. affects both men and women.

. not Contagious.

Clinically :

1- Firm dirty warty greasy, brownish papules in affolicullar distribution, mainly in seborrhi area of trunk, face, scalp marigin & behind ea

2- hand changes

* punctate keratosis on palm & soles

* nail changes : longitudinal white ridges; Distal notches, Subungual Keratosis, nail splitting.

* ACroKeratosis verruciformis. like lesions.

3- oral mucosa :

white umbilicated or Cobble Stone papules

or leukoplakia like k patches on palate, tonge buccal mucosa

- Exacerbations: Steroids, ultraviolat & Sunlight.
- Complications: * ↑ Susceptability to herpes simplex & Pyogenic infection.
  * Kaposis Varicelliform eruption: Herpetic lesions on top of Chronic Skin disease.
- association: Epilepsy, psychosis, ↓ delayed hypersensitivity reaction.
- Clinical types: ① verrucous Crusted malelorous plaques
  ② vesicular type.
  ③ unilateral liner lesion.
  ④ warty dyskeratoma
- Diagnosis: ① Clinically.
  ② histopathology

* hyperKeratosis * ACanthosis * papillomatosis.
* Chronic inflamatory infiltrate in upper dermis.
* ACanthalytic dyskeratosis → Corps ronds → in granular cell layer
  → Corps grains → in horney cell layer
* Suprabasal acanthdysis → Supra basal Lacunae.
* irregular upward proliferation of villi into the Lacunae.

*Acantholytic dyskeratosis (Corps ronds)

Central homogenous, basophilic pyknotic nucleus - small condensed nucleus surrounded by clear halo, peripheral to the halo lies basophilic dyskeratotic material.

DD:- ① Seborrhic dermatitis.

② acanthosis nigricans.

③ warty nevi

④ Hailey. hailey (Familial Benigen Pemighus)

Treatment :-

① oral retinoids 0.5-1 mg/kg/day

② Topical retinoids.

③ Dermabrasion.

④ Chemical peeling.

⑤ CO_2 laser

⑥ vit A & E.

⑦ Antibiotic & antiviral.

⑧ essential fatty acids

⑨ Cyclosporin.

WEEK 20

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q9

Q: Clinical Features of Darier's ds ?

Firm, warty, greasy, scaly, brown papules in afollicular distribution mainly in Seborrheic Sites as

Face, Scalp margins, neck, behind ears and groins.

Verrucous crusted malodorous plaques occur mainly in Intertriginous area. Thigh and face

- Hand Changes (pathognomonic).
- acrokeratosis verruciformis on dorsum of hand.
- punctate Keratosis on palm and soles.
- Nail Changes: Red or white longitudinal band - distal angular notch, splitting of nail plate - fragility, Subungual Keratoses.

1

Geno (Q 10)

D.D of Dorier disease?

(A) sever seborrheic dermatitis →

- Dorier is distinguished by +ve family history, involvement of Acral skin, nail, oral mucosa & and characteristic histological feature

(B) D.D of Dorier with Flexural affection:

① pemphigus vegetans (Hallopeau type)

- older age
- Histology show acantholysis with esinophil
- DIF show intercellular pattern of Pemphigus
- Antidesmoglein Ab by ELISA

Geno Q(10) D.D of Dario

[2]

[2] Hailey- Hailey disease :

- may be difficult to distinguish Clinically intertriginous Darier
- palmo planter papule / longitudinal erythro. nychia
- distal notching of nail - mucosal lesion
- prominent dyskeratosis - Acantholysis are characteristic of Darier disease.

[3]- Blastomycosis - like pyoderma :

neutrophilic infiltrate, No acantholysis and -ve DIF

④- Grover's disease :

In Grover's disease, pruritic Crusted papule are not confluent, and they develop after occlusion or sweating.

3

Gene & Io (DD) of Darier)

d) Acrokeratosis Verruciformis of Hopf

- Autosomal dominant.
- Clinically indistinguishable from Darier (Both have flat topped wart like papule on dorsal aspect of extremities)
- Histologically - this condition lacks acantholysis and dyskeratosis

	Darier's Disease	Epidermodysplasia verruciformis
Clinically	- Rare A-D - Mutation of ATP_2A_2 gene - Age 6 – 20 years ⊙ papules → Keratotic crusted red to brown with seborrheic Distribution. ⊙ May be confluent ⊙ palmoplantar affection ⊙ Small hypomelanotic macules in dark patients ⊙ Intertrigenous Lesions ⊙ Nail changes → Longitudinal red and white lines + V shaped notches. ⊙ oral manifestation :- Painless whitish papules	Rare A.R HPV 5, 8 childhood ⊙ Long standing, wide spread Flat, wart like lesions on arms, Legs, Face, back of hands ⊙ Macular erythematous P.V Like lesions on face, neck, arms ⊙ May be confluent ⊙ Malignant transformation in 50 %
	• Acantholysis → Supra-basilar • DysKeratosis → - Corps ronde - Corps grai - Papillomatosis - Hyper Keratosis - perivascular inflammatory infiltrate	→ Mild Hyper Keratosis + Acanthosis → Keratinocytes Contain perinuclear halos and blue-grey pallor → Atypical cell are present

q11

Palmoplantar keratoderma (PPK)

(A) Acquired palmar keratoderma

(1) Diffuse PPK

It appears in early infancy as a sharply demarcated diffuse PPK usually with a margin of erythema

(2) PPK with oesophageal Carcinoma

(3) Hereditary epidermolytic PPK

- histology: early shows epidermolytic hyperkeratosis

- clinically like diffuse PPK

(4) PPK punctata - which has multiple keratotic papules which may be linear

(5) PPK striata

(6) Mutilating PPK: Diffuse PPK keratosis of dorsal surface of hands diffuse keratosis on elbows and knees. It may be associated with hearing loss and scarring alopecia

التاريخ / / اليوم عنوان الدرس

(7) progressive PPK — D: ffuse PPK
occurs in infancy and increases in severity and extent with age.
Irregular keratotic patches may occur on arms and legs.

(8) Focal PPK + oral hyperkeratosis

[B] Recessively inherited forms

(1) keratosis palmaris et plantaris showing diffuse involvement of the palms and soles soon after birth and progression to the dorsa of the hands and feet, the ankles and wrists, physical and mental retardation.

(2) The papillon le Fevre syndrome clinically like type (I) in association with periodontosis resulting in the loss the deciduous teeth and later of permanent teeth.

* Treatment: oral retinoids.

Etretinate 0.5-1 mg/kg/day

Q13. (G.13).
Clinical types of hereditary palmoplantar Keratoderma. Discuss two of them?

A. Types:-
1. Diffuse:- → A Diffuse epidermolytic PPK.
→ B " non-epidermolytic " .
2. Focal:- → A Focal palmoplantar keratoderma with oral mucosal hyperkeratosis.
→ B Focal ppk without oral mucosal hyperkeratosis.
3. Punctate:- → Type 1: Keratosis punctata palmaris et plantaris (Autosomal dominant hereditary punctate keratoderma associated with malignancy).
Type 2: Spiny keratoderma.
Type 3: Focal acral hyperkeratosis.
4. Ungrouped:- → A Palmoplantar keratoderma & spastic paraplegia
→ B Palmoplanter keratoderma of Sybert.
→ C Striate PPK.
→ D Carvajal Syndrome.
→ E. Sclerotrophic syndrome of Huriez.
→ F. Vohwinkel syndrome.
→ G. Olmsted syndrome.
→ H Aquagenic keratoderma.

B. Discuss two:-

1. Diffuse PPK (epidermolytic):-

Its one of the most common patterns of PPK, an autosomal dominant condition that presents within the first few months of life, characterized by a well-demarcated, symmetric thickening of palms & soles, often with "dirty" snakeskin appearance due to underlying epidermolysis.

Diffuse

2. Non-epidermolytic :-

It is an autosomal dominant condition & is present from infancy, characterized by a well-demarcated, symmetric, often "waxy" keratoderma involving the whole of the palms & soles.

(14) PoroKeratosis → autosomal dominante condition

it is a specific disorder of Keratinization that is characterized histologically by presence of (Coronoid Lamella) Coronoid Lamella is a thin Column of closely stacked parakeratotic cells extending through the Stratum Corneum.

types

① plaque type (porokeratosis of mibelli)

Ach by one or more atrophic plaques.

Surrounded by raised wall, they may show gross overgrowth and even horn-like structure.

② Disseminated Superficial porokeratosis.

small & shallow furrow on trunk, Sole & palm.

③ superficial disseminated Actinic form

it is the most Common in Sunexposed areas

④ Linear form

⑤ tender form. is punctate form.

⑥ PoroKeratosis palmaris plantaris.

Histopathology: "Seen at the edge only"

1. hyperkeratosis
2. normally staining cells
3. poorly staining parakeratotic stratum corneum (Cornoid lamella)
4. the underlying cells shows pyknotic nuclei with perinuclear edema.

Treatment

* excision
* Liquid nitrogen.
* Topical 5-fluorouracil
* Topical v.t D_3 analogues.
* Sunscreen in actinic type

Q 15. Histopathology of parakeratosis of mibelli ?

from prephral Raised Ridge: Showing in it's Centre akeratin Filled Invagination - In the centre of which rises parakeratotic Column Called Cornoid lamella, base showing epidermal Cells that have pikenotic nuclei & perinuclear edema.

16- Geno :-

DNA instability syndrom? → Xeroderma Pigmentosum
→ cockayn's syndrom
→ Bloom's syndrom

① Xeroderma Pigmentosa

* it is AR characterized by extrem Cutanous photosenstivity
+ early develop of cutanous Malignancy
+ severe ocular lesion
+ neurological complication
+ abnormal DNA repair due to defeciancy of DNA endonuclease.

* clinical Picture :-

3 Stage → 1st → diffuse erythma and scaly on sun exposed area
→ 2nd → Poikiloderma → Atrophy of skin
→ solarkeratosis → mottled Pigmention
→ telangectisa
→ 3rd → malgnant tumor as keratoacanthoma, SCC, BCC

- ocular lesions → photophobia - conjunctivits - keretitis corneal opacity
- Neurologic abnormalitis → due to defective DNA repair in nerve cell resulting in neuronal death

* Histopathology

1st stage → - HyperKeratosis - thin stratum malpighi - accumulation of melanin in basal cell - ch inflam infiltration in dermis

2nd stage → as first stage ⊕ Basophilic degeneration of collagen (solar degeneration) in upper dermis simulate solar keratosis

3rd stage → Picture of malgnant tumors.

* ttt → sun screen - oral retinoids - oral Ca and vit D
- Excision of malgnant tumor.

② cockayne's syndrom :- AR - defective excision repair
- presented with :- photosenstivty, mental retardation, dwarfism, prepheral neuropathy, sunken eye - prominant ear, retinits Pigmentosa, dental caries, thining hair - basal ganglia calcification.

16 Geno

(3) Bloom's syndrom

- AR due to mutation in BLM gene
- Present with - Butterfly rash - immune deficiency
  - ↓ IgM - leukemia - photosensitivity
  - growth retardation.

Q17

Nail changes in darier's disease

1- Red or white Longtudinal bands.

2- distal angular notches

3- splitting of nail plate.

4- Fragility or subungual keratosis

Nail changes in ~~Koenen's~~ Tumor Tuberous sclerosis.

1- Longtudinal groove with out visible tumor

2- koenen's tumor

- non traumatic
- subungual or periungual
- Fibroma
  - rounded soft, rounded papule
  - more in toes
  - pointed, hyper keratotic papule

Genetics

18- eye manifestation of neurofibrometosis - Pseudo Xanthoma elasticum. ?

* eye manifestation of PXE

- Angioid streaks of fundi of the eye - this occure due to calcification of elastic fibers in lamina elastica → fissure and repeated Hge and exudates → degenerative change in retina → progressive loss of vision.

* eye Hainfestation of Neurofibrometosis

1- lisch nodules → melanocytic hemartoms appear as dome shape usually bilateral lesion ove the iris it is found in 90% of Pattant.

2- optic gliomas (most common CNS tumor in NF-1 → optic atrophy.

3- proptosis and Ptosis -

4- Congenital glucoma-

Ehler danlos syndrome.

Etiology:-

① mutation in genes encoding structural (ECM) proteins

② Collagen component of elastic fibrobers, enzymes that modify structural protcins.

C.P

- Cutaneous manifestation include.
  - hyper extensible skin
  - Fragile skin
  - easy bruising
  - poor wound healing with atrophic scars
- hyper mobility of joints which may Lead to dislocations.

clinical variant 10

- At least $\frac{1}{2}$ of affected individuals can touch tip of nose with their tongue (Gorlin's sign)

dd with other Causes of Lax skin Q19-2

1- Ageing

2- marked weight Loss

3- Elasto Lysis

• Generalized	Localized
• Congenital • Acquired :- with SLE, multiple myeloma, penicillamine therapy	• Aneto derma. • Blepharo chalasis • chronic atrophic acrodermatitis • granulomatous slack skin (due to lymphoma).

(دى dd اللى موجودة فى عاصم لو حد عنده حاجه زيادة يضيفها وينزلها على الجروب)

[1]

Mastocytosis

* Mast cell hyperplasia that affect the skin &/or organs

* Mast cells ظبش
Develop in bone marrow → enter blood (immature form).
Mature mast cell. ظبش لـ بيوجد بالدم

* عندها receptors زي
(tyrosine kinase, KIT, CD117).

الـ KIT receptor في { Mast cell / Melanocyte } و نفس الـ receptor
علشان كدة بيحصل صبغيولوة mastocytosis

* Mast cell activated by stem cell factor ⇐ fibroblasts (تنتج)
⇓
stimulate cell growth.

In mastocytosis المرض الكبير ظبش

Pathogenesis: Autoactivating mutation of KIT receptor genes.

⇒ KIT receptor stimulation ⇒ Mast cell Proliferation mastocytosis
with Release of mast cell mediators ⇒ histamine, ...
∴ Sign & Symptoms of Disease

2

WHO classification

- Cutaneous mastocytosis associated with hyperpigmentation (4)
  1- UP urticaria pigmentosa
  2- Mastocytoma
  3- TMEP (Telangrectasia macularis eruptive perstans.
  4- Diffuse cut. mastocytosis (childhood mastocytosis).
- Systemic mastocytosis (4)
  1- Indolent systemic mastocytosis
  2- Aggressive systemic mastocytosis
  3- Mast cell leukemia
  4- systemic mastocytosis with Associated clonal hematological non-mast cell disease (AHNMD)

1 UP urticaria pigmentosa

- Most common in children. 65%
- Tan → Brown macules → Patches or Papule. Solo-lesions
- Site ⇒ Trunk & proximal extremities

2 Mastocytoma.

- 2nd most common in children - At birth or during infancy
- Solitary tan, yellow or brown plaque or nodule.
- Site ⇒ Distal extremities

3 Diffuse Cutaneous mastocytosis

Diffuse
- Numerous red to yellow → tan papules & plaques → leathery take
- Marked thickened skin with Distorted facial features.

[3]

[4] Telangiectasia macularis eruptiva perstans.

- Very rare.

Important

⇒ telangiectatic macules without hyperpigmentation

Diagnostic Sign of Cutaneous Mastocytosis

[Darier's Sign]

[1] lesion تورم وأحمر

⇒ urticarial (wheal) at lesion site.

due to release of mast cell mediators.

[2] Concentration of mast cell in lesion.

- Mastocytomas } 150 - 40 fold greater than
- childhood UP } normal skin

- Adult UP → 8 fold mastcell greater than normal skin

[4] Systemic Mastocytosis

- May be asymptomatic
- if present due to mast cell mediators (heparin, histamine, ...
- Bone → osteoporosis → bone pain.
- GIT → liver, spleen, LN → enlargment
  epigastric pain, diarrhea.

* Mastocytosis Syndrome

* Episodes of Pruritis, headache, flushing tachycardia, hypotension.
* Skin lesion, bone lesion & hepatosplenomegaly
* Related to histamine release.

Investigation

Direct (Skin, internal organ bopsy

[1] Skin Biopsy

a) H&E : Most cell infiltrate in dermis ± eosinophil mainly in papillary dermis as mastcell locate around blood vessels.

- in Diffuse cut & mastocytoma → Round cell with Fried egg appearance
- in UP & TMEP → spindle shaped cells

b) Special stain Giemsa. Cytoplasm contain meta chromatic granules ⇒ Purple

[2] Immunohistochemistry : monoclonal AB → tryptase or CD117 (CKIT)

[3] Molecular diagnosis Detect KIT gene mutation

Indirect

1- In Blood.

* Serum tryptase > 20 ng/mL
* Plasma IL 6.

2- in urine

- histamine & its metabolites
- PGD_2 metabolites

[5]

Treatment

[1] Avoid aggravating factor.

- Physical - exercise, heat - local trauma to skin
  narcotics, Salicylates, Polymyxin B.

[2] No cure for this Disorder.

[3] local treatment.

- Potent & Superpotent Corticosteroids.
- intralesional C.S.

[4] Systemic ttt

- oral H_1 & H_2 receptor antagonist.
- oral Cromolyn Sodium (mast cell stabilizer).
- oral PUVA
- oral Corticosteroids.

[5] Biologic therapy :-

KIT inhibitors Imatinib mesylate.

Scanned by CamScanner

Gend 21 Date ①

Q2 / Clinical picture? h/p of Childhood Cutaneous Mastocytosis

① Clinical picture:

→ Multiple [50-100 lesion], small reddish-brown, hyperpigmented macules & papules
- Nodules & plaques: less frequent.

→ occur common on trunk. & may on extremities, head & neck.

→ lesion urticate on stroking [Darier's Sign] due to higher density of mast cells. followed by refractory period. for 2-3 day ē -Ve darier sign.

→ Vesicles & bulla containing clear fluid → bullous or ē pigmented lesion → bullous mastocytosis

(4) Histopathology:

→ Mast cell infiltration
ē characteristic metachromatic granules in their cytoplasm
ē Giemsa or toluidine blue.

« Care must be taken to avoid urtication of the lesion during biopsy

→ Perivascular mast cell infiltrate in upper dermis

→ increased epidermal pigmentation ē presence of melanophages in upper dermis

(1) In diffuse mastocytosis, dense, band like subepidermal mast cell infiltrate appears

Gen.

22- Adut onset ichthyosis?

--Adult onset ichthyosic (acquired ichthyosis

Def :- Accumulation of visible scale on the skin surf

Cause:-

1- Malignancy (Paraneoplastic) lymphomas mainly Hodgkin's disease but may be ē other lymphoma, multiple myeloma carcinoma and kaposis sarcoma.

2- Nutritional deficancy * Malnutrition * vit A deficancy * esstinal fatty Acid

- -deficancy of linoleic Acid → distwb barrier function
- deficancy of arachidonic acid → proliferative abnormality → scale erythma.

3- drugs as hypocholesterolemic agent

4- enviroment → xerosis

5- immunological → SLE . dermatomyositis

6- endocrinal → hypothyroidism

7- infection → leprosy - HIV infection

8- sarcdosis

+++ :-

1- symptomatic managment to reduce scale.

- continous use of lubricant and emollient
- Ceramide conting lipid cream → effective
- Praparation conting urea and keratolytic
- Moisturizing cleansers and humidfiers.

2- topical retinoid

3- vit D cunalogues

4- oral retinod as acitretin.

Q. 23

Diagnostic Criteria for Tuberous Sclerosis.

- Major
  - Cutaneous
  - extracutaneous.
- Minor.
  - Cutaneous.
  - extracutaneous.

* Definite tuberous sclerosis:.
  2 major OR 1 major + 2 minor.
* Probable TS:- one major + 1 minor
* Possible TS:- either 1 major OR 2 or more minor features.

	Major features.	Minor.
Cutaneous.	- Facial Angiofibromas. - ungual or Periungual Fibromas. - ≥ 3 Hypomelanotic macules - Shagreen Patch. (Collagenoma)	- Confetti hypopigmented skin lesions.
Extra-Cutaneous	- Multiple retinal nodular hamartomas - Renal angiomyolipoma. - Subependymal nodules. - Subependymal giant cell astrocytoma - Cardiac rhabdomyoma. - lymphangioleiomyomatosis	- Retinal achromic Patch - Multiple renal cysts. - Bone cysts. - Gingival Fibromas. - Multiple pits in dental enemal. - Hamartoma Rectal Polyp - Cerebral white matter radial migration lines

GH

q24

Pitted keratolysis	Punctate keratoderma
- Superficial infection of skin caused by Corynebacterium → keratin degrading proteases - Numerous superficial erosions in st. corneum of sole - Hyperhidrosis	- AD Genodermatosis in which there is hyperkeratosis of skin of palm & sole - Multiple, tender, keratotic papules on palm & sole
ttt - Topical sodium fusidate ointment - Erythromycin or clindamycin - ttt of hyperhidrosis	- Topical: 1- Salicylic acid 2- Lactic acid & urea 3- Mechanical debridement - Systemic: 1- Oral retinoids 2- Ttt of 2ry fungal & bacterial infection

Gene

Q25 (G.25)
Histopathology of mastocytoma?

1. There are increased numbers of mast cells in the dermis of all types of cutaneous mastocytosis.

2. Increase in melanin in epidermis.

3. The mast cells are usually oval or spindle-shaped & have granules that stain metachromatically with toluidine blue. They are also well demonstrated by Giemsa or chloroacetate esterase stains in formalin-fixed biopsies.

4. Mast cell infiltrates are predominantly found around blood vessels & skin appendages.

5. A small increase in numbers of mast cells has been found in non-lesional skin of urticaria pigmentosa.

6. Full-thickness infiltration of skin or a band-like involvement of the upper dermis are seen in mastocytomas.

7. Bone marrow involvement typically presents with focal aggregates of mast cells, although infilteration may be diffuse & spindle shaped & is often accompained by increased numbers of immature neutrophils, macrophages, eosinophils & lymphocytes. (& sometimes fibrosis.

	Ichthyosis Vulgaris	Recessive X-Linked (RXLI)	Epidermolytic Ichthyosis	Congenital Ichthyosiform Erythroderma CIE	Lamellar Ichthyosis	Harlequin Ichthyosis.
Epidemiology	AD	X-Linked "boys only"	AD	AR Rare	AR Rare	AR Rare
Incidence	→ Common	un Common	Rare			- Born: prematurely incased in hard, thick stratum corneum
onset	→ 3-12 month	→ < 3 month	→ At birth → generalized erythema with blistering	→ Birth "Collodion baby" Few week later the collodion membrane Cracks, peels off in sheets → May improve. → persist		• Fatal within 1st week of life
Course	→ Improve	→ persist	→ May improve			
Clinically Scales	Small, Fine, shiny white, translucent	Large, dark brown, dirty tightly adherent	Thick, brown, Verrucous spiny (Cobblestone pattern)	Fine, white with pronounced erythroderma	Large, thick, dark plate like with no or mild erythroderma.	Cracks in the hard, thick st. Corneum lead to larg yellow adherent plates separated by board, deep, red fissures. lead to water loss, heat, electrolyte imbalance, infection
Distribution	Extensors sparing Flexures due to Humidity - Hyperlinear palm / sole - Furrowed heels	More generalized (Trunk, neck, Flexures sparing Face	Generalized with flexural accentuation Furrow hyper Keratosis	Generalized	Generalized affect face, Flexurals.	• Death within Few days Cause of Respiratory infection or Resp Insufficiency.
Associations	ATopy 50% Keratosis pilaris PPK mild	Corneal opacity 50% cryptorchism prolonged Labour in Carrier Female.	• infection in flexural areas Foul odar - PPK sever - nail dystrophy - Gait, posture abnormalities	scaring Alopecia - PPK - Heat intolerence - Ectropion	sparse scalp hair PPK Clumpled ears Marked ectropion hypo hidrosis. - chanarin - ~~Dof~~ Dorfman Syndrome	• Improved prenatal care + Oral retinoid → prolong survival
						Associations Marked ectropion Eclabium Flattened ears Hand, foot edema, swollen Auto amputation due to Constricting skin bands.
Histopathology	- Moderate Hyper Keratosis - Thin or Absent Granular layer - EM Abnormal Keratohyaline granules	- Hyper Keratosis - Normal or thick Granular layer EM Abnormal odland bodies.	Epidermolytic Hyper Keratosis	Marked hyper Keratosis parakeratosis, Acanthosis hyper granulosis. PAS & Lectin +ve of st. corneum EM ↑ Number of lamellar bodies • Accumulation of lipid droplet in st. Corneum • Dis organized intercellular Lipid Lamellae	Compact hyper keratosis Normal Granular layer mild acanthosis PAS, lectin -ve	HP extraordinary thick st. Corneum with Follicular hyper Keratosis EM Absent or abnormal lamellar granules Absence of Lipid Lamellae
Diagnosis	C/P * ↓ st. granulosum * ↓ FLG immunostaining * Molecular testing	* lipoprotein electrophoresis:- ↑ mobility of B-Fraction * ↑ plasma cholesterol sulfate * Molecular Testing FISH & array CGH	C/P H/P Molecular testing	C/P + EM + Molecular testing In situ tranglutaminase assay	Diagnosis the same • Defect in transglutaminase → abnormal cell envelope	Dx Concentric accumulation of Keratotic material around hair shaft - is diagnostic in 2nd trimester of life
pathogenesis	**Retention Hyper Keratosis**		**Hyperproliferative Hyperkeratosis**	Mutation in TGM1, ALOXE3 ALOXE12B	• Mutation of TGM1 ABCA12	Pathogenesis ~~Abnormal~~ Loss of function mutation of in the ABC Transporter gene ABCA12
	Cell Kinetic → Normal ↓ serine protease → resist Dsg1 → resist desmosome → Retention Hyper Keratosis Mutation in FLG → ↓ Filaggrin → impair barrier → water loss → xerosis	→ Normal Deletion of STS gene → ↓ Steroid Sulfatase → ↑ cholesterol sulfate → ↓ transglutaminase → ↓ desquamation → Retention Hyper Keratosis	increased point mutation of KRT1 and KRT10 → impair mechanical Stability of epidermis. → failure of desquamation	Cell Kinetics → increased ↑ in n-alkanes (Hydrocarbon) in scales	Cell Kinetic Normal Normal n-alkanes ↑ sterol, Fatty acid in Scales	